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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/307,223	Applicant(s) Varner et al
	Examiner Ungar	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 7, 2001*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-5, 9-14, 55-72, 75, and 80-120* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-5, 9-14, 55-72, 75, and 80-120* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

1. The Amendment filed September 7, 2001 (Paper No. 11) in response to the Office Action of March 9, 2001 (Paper No. 9) is acknowledged and has been entered. Previously pending claims 6-8, 15-18, 21-54, 73-74 and 76-79 have been canceled and new claims 80-120 have been added. Claims 1-5, 9-14, 55-72, 75 and 80-120 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The following rejections are being maintained:

Claim Rejections - 35 USC § 112

4. Claim 2 remains rejected under 35 USC 112, second paragraph for the reasons previously set forth in Paper No. 9, Section 6, pages 4-5.

Applicant argues that the meaning of "substantially" is clear based on the recitation, in the specification, of a mathematical range as well as a control to apprise the artisan of the exemplary preferred mathematical ranges for binding of the ligand to alpha 5 beta 1 integrin as compared to the binding of the ligand to another integrin. The argument has been considered but has not been found persuasive because the statements within the specification, drawn to range, are not limiting. Further, Applicant is reminded that the claims define the subject matter of his invention and that the specification cannot be relied upon to read limitations into the claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Applicant's arguments have not been found persuasive and the rejection is maintained.

Claim Rejections - 35 USC § 102

5. Claims 1-5, 9-13, 55-66, 68-69, 71-72 and 75 remain rejected under 35 USC 102(e) and newly added claims 80-120 are rejected under 35 USC 102(e), essentially for the reasons previously set forth in Paper No. 9, Section 8, pages 5-8.

It is noted that Examiner previously made clear that the definition of "peptide" is not limiting, thus it is assumed for examination purposes that a peptide includes any molecule which is a polymer of amino acids linked by a peptide bond which reads on sFN.

Applicant argues that Pasqualini et al (US Patent No. 5,922,676) does not anticipate the instant invention because (a) Examiner concedes that Pasqualini et al does not recite the limitation that "the agent interferes with the specific binding of alpha 5 beta integrin to a ligand", that "the ligand is fibronectin, "agent does not substantially interfere with the specific binding of a ligand to an integrin other than alpha 5 beta 1, (b) in the absence of express anticipation, the Examiner must show that each and every element of the claimed invention is disclosed under principles of inherency and that the law is clear that in relying upon the theory of inherency, the Examiner must provide a basis in fact and/or technical reasoning to support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the prior art and no such evidence or reasoning was advanced in support of the position that the claimed method appears to be the same as that of the prior art method, © the instant claim limitations do not "necessarily" flow from the teachings of the applied prior art in that (I) Pasqualini discloses inhibiting metastases by administering superfibronectin, (ii) Pasqualini discloses that sFN

"may" ameliorate .....angiogenesis and Applicant argues that, although fibronectin binds alpha 5 beta 1 integrin, that it also binds other receptors which have a proven role in angiogenesis and it is probable that this inhibition may result from sFN's interference with the binding of any one or more of the other receptors and therefore does not necessarily interfere with specific binding of alpha 5 beta 1 integrin to a ligand, (iii') cell attachment to sFN is mediated by both integrins and other distinct receptors, (iv') the *in vitro* results of Pasqualini et al, drawn to cell migration on collagen are different than that taught in the instant specification, (v) as drawn to claim 3, fibronectin is only one of several ligands which bind to alpha 5 beta 1 integrin so that the inhibition of specific binding of alpha 5 beta 1 integrin is not the only mechanism for reducing or inhibiting angiogenesis as recited in the claimed methods and in view of the alternative pathways for inhibiting angiogenesis, it cannot be concluded that sFN mediated inhibition of angiogenesis must necessarily be the result only of interference with specific binding of the alpha 5 beta 1 integrin to fibronectin, (d) Pasqualini discloses inhibiting metastases by administering peptides and relates peptides to inhibiting metastases

The argument has been considered but has not been found persuasive because (a') although Applicant was invited to submit objective evidence demonstrating that the claimed method is functionally different than that taught by the prior art and to establish patentable differences, this evidence has not been submitted, (a') and (b') given that the invention is drawn to a method of ameliorating angiogenesis and treating pathologies with angioproliferative components comprising administering superfibronectin and that the ligand is a multimeric form of fibronectin, the

superfibronectin would be expected to bind to a fibronectin receptor, known to be alpha 5 beta 1 and that binding would by its very nature would interfere with the specific binding of alpha 5 beta 1 integrin to another ligand and since fibronectin is specific for alpha 5 beta 1, it would also be expected to bind with greater affinity and avidity to that integrin as opposed to other integrins and given the indefinite nature of the term "substantially", it would not be expected to substantially interfere with the specific binding of a ligand to an integrin other than alpha 5 beta 1, (b') Examiner has not relied upon the theory of inherency, the ligand of the prior art is a form of fibronectin, that is a multimeric form, which binds to the claimed integrin receptor, (c')(I') as previously disclosed, Pasqualini specifically teaches that the invention provides a method of ameliorating angiogenesis and treating the angioproliferative component of a pathology by administering sFN and clearly teaches that stimulation of blood vessel growth and the conversion of a tumor to an angiogenic phenotype involves a change in the local balance of blood vessel growth inhibitors and growth stimulators and that the invention provides for a general method of inhibiting angiogenesis and cytokine-mediated endothelial cell growth and migration (see Example X, cols 27 and 28), (c')(ii') Applicant admits on the record that sFN interfers with the binding of 5 different receptors on endothelial cells, including alpha 5 beta 1, to their respective ligands and for the reasons set forth above, sFN would interfere with the specific binding of a ligand to alpha 5 beta 1 integrin, (c')(iii) Applicant again admits on the record that sFN binds to the alpha 5 beta 1 integrin receptor, Applicant is invited to submit objective evidence to establish that the method of the prior art does not possess the same material

structural and functional characteristics of the claimed method, (c')(iv') Applicant is arguing limitations not recited in the claims as currently constituted, (c')(v') while not the only possible method, the prior art meets the limitations of the claims for the reasons set forth previously and above, Applicant is invited to submit objective evidence to establish that the method of the prior art does not possess the same material structural and functional characteristics of the claimed method, (d') as previously disclosed, the specification broadly defines the term "peptide' as a polymer of amino acids that are linked by peptide bonds and for the reasons previously set forth this definition is not limiting and sFN meets the limitation of this claim since it is a polymer of amino acids that are linked by peptide bonds. Applicant's arguments have not been found persuasive and the rejection is maintained. Applicant is again invited to submit objective evidence to establish that the method of the prior art does not possess the same material structural and functional characteristics of the claimed method.

New Grounds of Rejection

Claim Rejections - 35 USC § 102

6. Claims 1-3, 9-13, 55, 57-63, 65-66, 71-72 and 75,80-97, 100-106, 108- 117, 119-120 are rejected under 35 U.S.C. § 102(e) as being anticipated by US Patent No. 5,922,676 as evidenced by WO95/14714.

For the reasons set forth previously and above, it is assumed for examination purposes that a peptide includes any molecule which is a polymer of amino acids linked by a peptide bond which reads on sFN.

US Patent No. 5,922,676 teaches as set forth previously and above and further teaches that the administration of sFN causes regression of established primary tumors *in vivo* (see Example VII). WO95/14714 further teaches that the known alpha and beta subunits of integrins associate in various combinations to form at least twenty receptors with different ligand specificities (p. 1, lines 10-15) and that fibronectin is a ligand that is specific for alpha 5 beta 1 receptor in that alpha 5 beta 1 is the fibronectin receptor (page 2, lines 3-5) and specifically teaches that a molecule "selectively binds to an integrin if it binds with a 10-fold or higher affinity to that integrin as compared to another integrin and that a peptide is "specific for" an integrin if it binds to that integrin with a 100-fold higher affinity as compared to another (p. 12, lines 18-25). Given that alpha 5 beta 1 is the fibronectin receptor, it would be expected that fibronectin not only selectively binds to alpha 5 beta 1 but also that it is specific for alpha 5 beta 1 and that thus all of the limitations of the claims are met. Although the reference does not specifically state that the agent of the method binds alpha 5 beta 1 integrin at least two-fold, five-ten fold, ten fold greater than any other integrin, alpha V beta 3, the claimed method appears to be the same as that of the prior art method absent a showing of unobvious differences. The office does not have the facilities for examining and comparing applicant's method with the method of the prior art in order to establish that the method of the prior art does not possess the same material structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed method is functionally different than that taught by the prior art and to establish patentable

differences. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat.App. & Int.).

Further, the method of the prior art comprises the same method steps as claimed in the instant invention, that is, administering an agent, which binds alpha 5 beta 1 integrin (which is expected to interfere with the specific binding of endogenous ligand to alpha 5 beta 1 integrin for the reasons of record) to the same population, that is to a tissue/individual, with a neoplasm, carcinoma, metastasis, thus the claimed method is anticipated because the method will inherently lead to reducing or inhibiting angiogenesis. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

7. Claims 80-106, 108- 117, 119-120 are rejected under 35 U.S.C. § 102(e) as being anticipated by US Patent No. 5,922,676 as evidenced by WO95/14714 and Pytela et al, Cell 1985, 40:191-198, IDS item.

The claims are drawn to the methods of claims 1, 55 and 57 wherein the binding of the agent to alpha 5 beta one is at least two-fold, five-ten fold, ten fold greater than the binding of said agent to an integrin other than alpha 5 beta 1 integrin wherein said integrin is alpha V beta 3 integrin.

US Patent No. 5,922,676 as evidenced by WO95/14714 teach as set forth above. Pytela specifically teaches that alpha 5 beta 1 is selective for fibronectin. WO95/14714 further teaches that the known alpha and beta subunits of integrins associate in various combinations to form at least twenty receptors with different ligand specificities (p. 1, lines 10-15) and that fibronectin is a ligand that is specific for alpha 5 beta 1 receptor in that alpha 5 beta 1 is the fibronectin receptor (page 2,

lines 3-5) and specifically teaches that a molecule that "selectively binds to an integrin if it binds with a 10-fold or higher affinity to that integrin as compared to another integrin and that a peptide is "specific for" an integrin if it binds to that integrin with a 100-fold higher affinity as compared to another (p. 12, lines 18-25). Given that alpha 5 beta 1 is the fibronectin receptor, it would be expected that fibronectin not only selectively binds to alpha 5 beta 1 but also that it is specific for alpha 5 beta 1 and that thus all of the limitations of the claims are met. Although the reference does not specifically state that the agent of the method binds alpha 5 beta 1 integrin at least two-fold, five-ten fold, ten fold greater than any other integrin, alpha V beta 3, the claimed method appears to be the same as that of the prior art method absent a showing of unobvious differences. The office does not have the facilities for examining and comparing applicant's method with the method of the prior art in order to establish that the method of the prior art does not possess the same material structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed method is functionally different than that taught by the prior art and to establish patentable differences. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat.App. & Int.).

Claim Rejections - 35 USC § 103

8. Claims 1-5, 9-13, 19-20, 55-72, 75, 80-106, 108- 117, 119-120 are rejected under 35 U.S.C. § 103 as being unpatentable over US Patent No. 5,922,676, of

record as evidenced by WO95/14714, of record and Thorpe, of record and Pytela et al, Cell, 1985, 40:191-198, IDS item).

For the reasons set forth previously and above, it is assumed for examination purposes that a peptide includes any molecule which is a polymer of amino acids linked by a peptide bond which reads on sFN.

The claims are drawn to a method of reducing or inhibiting angiogenesis in a tissue, in an individual, reducing the severity of a pathological condition associated with angiogenesis in an individual, comprising contacting alpha 5 beta 1 integrin in the tissue with an agent that interferes with specific binding of the alpha 5 beta 1 integrin to a ligand expressed in the tissue, thereby reducing or inhibiting angiogenesis in the tissue, wherein the agent does not substantially interfere with the specific binding of a ligand to an integrin other than alpha 5 beta 1 integrin to its ligand, wherein the ligand is fibronectin, wherein the tissue comprises ocular tissue, wherein the ocular tissue is selected from the group including retina, macula and cornea, wherein the tissue comprises a neoplasm, wherein the neoplasm is malignant, wherein the neoplasm is a metastatic malignant neoplasm, wherein the neoplasms is a carcinoma, a sarcoma, wherein the agent comprises a peptide, wherein the agent is linked to a cytotoxin, chemotherapeutic drug, wherein the individual is a human, wherein the carcinoma is selected from the group including breast carcinoma, colon carcinoma, ovarian carcinoma and pancreatic carcinoma, wherein the malignant neoplasm is a sarcoma, wherein the agent is administered iv, administered orally, wherein the agent is administered into a neoplasm, wherein the pathological conditions are selected from the group including diabetic retinopathy

and macular degeneration by neovascularization, wherein the agent is administered in the form of eye drops, wherein the agent is administered at a dose of 0.0001 to 100 mg/kg of body weigh, wherein the claims are further drawn to the methods of claims 1, 55 and 57 wherein the binding of the agent to alpha 5 beta one is at least two-fold, five-ten fold ten fold greater than the binding of said agent to an integrin other than alpha 5 beta 1 integrin wherein said integrin is alpha V beta 3 integrin.

US Patent No. 5,922,676, WO95/14714 and Thorpe teach as set forth previously and above but do not teach the peptide linked to a cytotoxin, wherein the cytotoxin is a cancer chemotherapeutic drug, wherein the agent is administered into a neoplasm, wherein the agent is administered by eye drops.

Pyetela et al teach that alpha 5 beta 1 is selective for fibronectin (see abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to link the agents of US Patent No. 5,922,676 to a cytotoxin using the method taught by Thorpe. One of ordinary skill in the art would have been motivated to produce the claimed cytotoxin-linked agents in view of the teachings that such cytotoxin-linked agents are useful for diagnosis of refractory tumors and the general knowledge that antibodies can be successfully targeted to tumor cells. Given that some of the methods of US Patent No. 5,922,676 are drawn to treatment of pathologies with angiogenic components (cancer), it would have been *prima facie* obvious and one would have been motivated to use a cytotoxin that is a chemotherapeutic in order to target it to the tumor. Finally, it would have been *prima facie* obvious and one of ordinary skill in the art would have been

motivated to inject the agents of the combined references directly into the neoplasm/tumor in the methods of US Patent No. 5,922,676 in order reduce diffusion and non-specific sequestration of the agents.

It would have been *prima facie* obvious and one of ordinary skill in the art would have been motivated to administer the agent of the combined references for treatment of ocular pathology by administration of eye drops because US Patent No. 5,922,676 specifically teaches the topical administration of the agent of the invention.

Applicant's arguments drawn to the rejection of claims 1-5, 9-14, 19-20, 55-72 and 75 are relevant to the instant rejection.

Applicant (a) reiterates arguments discussed above drawn to Pasqualini et al, (b) argues that Thorpe lacks all of the limitations of the claims because Thorpe is silent on "reducing or inhibiting angiogenesis, © the prior art did not know that alpha 5 beta 1 integrin was associated with angiogenesis therefore there is no motivation to reduce or inhibit angiogenesis by interfering with the specific binding of an alpha 5 beta 1 ligand, (d) Pasqualini does not teach eye drops, but rather teaches topical administration, (e) none of the claims recite cytotoxin-linked agents, (f) none of the claims recite injecting agents directly into a tumor, (g) Examiner does not establish a reasonable expectation of success .

The arguments have been considered but have not been found persuasive (a') for the reasons set forth above, (b') Applicant has argued and discussed the references individually without clearly addressing the combined teachings. It must be remembered that the references are relied upon in combination and are not meant

to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which made up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in combination. In re Young, 403 F.2d 754, 159 USPQ 725 (CCPA 1968); In re Keller 642 F.2d 413,208 USPQ 871 (CCPA 1981), (c') Pasqualini et al specifically teach the inhibition of angiogenesis and treating pathologies with angioproliferative components by the administration of an agent as defined by the specification, wherein that agent was know to be a ligand for alpha 5 beta 1 integrin and was specifically shown to inhibit angiogensis, (d') for the reasons previously set forth, both the motivation and the mode of administration are obvious, (e') it is suggested that Applicant read claims 19, 20, (f') it is suggested that Applicant read claim 67, (g') given the teaching in Pasqualini et al and the specific exemplification of inhibition of angiogenesis in Pasqualini, one would have a reasonable expectation of success.

9. Claims 1-5, 9-14, 19-20, 55-72, 75, 80-120 are rejected under 35 U.S.C. § 103 as being unpatentable over US Patent No. 5,922,676, of record as evidenced by WO95/14714, of record.

The claims are drawn to a method of reducing or inhibiting angiogenesis in a tissue, in an individual, reducing the severity of a pathological condition associated with angiogenesis in an individual, comprising contacting alpha 5 beta 1 integrin in the tissue with an agent that interferes with specific binding of the alpha 5 beta 1 integrin to a ligand expressed in the tissue, thereby

reducing or inhibiting angiogenesis in the tissue, wherein the agent does not substantially interfere with the specific binding of a ligand to an integrin other than alpha 5 beta 1 integrin to its ligand, wherein the ligand is fibronectin, wherein the tissue comprises ocular tissue, wherein the ocular tissue is selected from the group including retina, macula and cornea, wherein the tissue comprises a neoplasm, wherein the neoplasm is malignant, wherein the neoplasm is a metastatic malignant neoplasm, wherein the neoplasms is a carcinoma, a sarcoma, wherein the agent comprises a peptide, wherein the peptide is SEQ. ID. NO:1, wherein the agent is linked to a cytotoxin, chemotherapeutic drug, wherein the individual is a human, wherein the carcinoma is selected from the group including breast carcinoma, colon carcinoma, ovarian carcinoma and pancreatic carcinoma, wherein the malignant neoplasm is a sarcoma, wherein the agent is administered iv, administered orally, wherein the agent is administered into a neoplasm, wherein the pathological conditions are selected from the group including diabetic retinopathy and macular degeneration by neovascularization, wherein the agent is administered in the form of eye drops, wherein the agent is administered at a dose of 0.0001 to 100 mg/kg of body weigh, wherein the claims are further drawn to the methods of claims 1, 55 and 57 wherein the binding of the agent to alpha 5 beta one is at least two-fold, five-ten fold ten fold greater than the binding of said agent to an integrin other than alpha 5 beta 1 integrin wherein said integrin is alpha V beta 3 integrin.

US Patent No. 5,922,676, of record as evidenced by WO95/14714, of record, teach as set forth previously and above. As previously disclosed, SEQ ID NO:18 of US Patent No. 5,922,676 is an alpha 5 beta 1 directed peptide and has

100% identity to SEQ ID NO:1 (see Paper No. 9, page 10). WO95/14714 teaches as previously disclosed, that SEQ ID NO:6 comprises SEQ ID NO:1 and SEQ ID NO:12 has 100% identity to SEQ ID NO:1 (see Paper No. 9, pgs 10-11). WO94/14714 further teaches that SEQ ID NO:12 allows the specific isolation of alpha 5 beta 1 integrin (p. 17, lines 8-10). It is noted that, given that the reference specifically teaches that specific binding means 100 fold greater binding than to any other integrin and that the isolation shown is specific, it is clear that SEQ ID NO:12 has 100 fold greater binding for alpha 5 beta 1 integrin than for any other integrin. The reference further teaches that because the peptides of this invention bind to certain integrins, they compete *in vivo* for the binding of integrins. Administered to an individual, they are useful for preventing binding of integrin-bearing cells with their target molecules in vivo (p. 19, lines 28-32).

It would have been prima facie obvious to substitute SEQ ID NO:12 of WO 95/14714 or SEQ ID NO:18 of US Patent No. 5,922,676 for the sFN of US Patent No. 5,922,676 in the method of US Patent No. 5,922,676 because WO95/14714 specifically teaches that the peptides of the invention compete *in vivo* for the binding of integrins and it would be expected that, given the definition in WO05/15715 that SEQ ID NO:18 or SEQ ID No: 12 would bind to alpha 5 beta 1 at least 100 fold greater than to any other integrin and thus would interfere with the specific binding of alpha 5 beta 1 integrin to endogenous fibronectin, one of ordinary skill in the art would have expected to successfully inhibit angiogenesis and treat pathologies with angioproliferative components by administering the peptide. Further, one of ordinary skill in the art would have been motivated to

substitute either peptide in the method of US Patent No. 5,922,676 because the peptides can be cheaply and easily synthetically produced.

Claim Rejections - 35 USC § 112

10. Claims 80-86, 90-96 and 110-116 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of an agent wherein binding of said agent to alpha 5 beta 1 integrin is at least two-fold, five fold, ten fold greater than the binding of said agent to an integrin other than alpha 5 beta 1, wherein said other integrin is alpha V beta 3 integrin has no clear support in the specification and the claims as originally filed. Applicant points specifically to page 23, lines 6-14 for support for the newly added limitations. A review of the suggested support reveals support for peptides that bind specifically to alpha 5 beta 1 as useful as antagonists of alpha 5 beta 1 binding to its ligands wherein the peptide binding to alpha 5 beta 1 integrin is at least two fold, five fold, ten fold greater than the said binding to an integrin other than alpha 5 beta 1 integrin wherein the other integrin is alpha V beta 3 integrin. The suggested support is not found persuasive for the broadly written claim because the support is drawn only to peptides and not to the broadly claimed "agent". The subject matter claimed in claims 80-86, 90-96 and 110-116 broadens the scope of the invention as originally disclosed in the specification.

11. Claims 86, 96 and 116 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of an agent which does not interfere with the specific binding of a ligand to an integrin other than alpha 5 beta 1 integrin has no clear support in the

specification and the claims as originally filed. Applicant points specifically to page 23, lines 6-14 for support for the newly added limitations. A review of the suggested support reveals support for peptides/antibodies that bind specifically to alpha 5 beta 1 as useful as antagonists of alpha 5 beta 1 binding to its ligands wherein the antagonists binding to alpha 5 beta 1 integrin is at least two fold, five fold, ten fold greater than the said binding to an integrin other than alpha 5 beta 1 integrin wherein the other integrin is alpha V beta 3 integrin. The suggested support is not found persuasive because there is nothing in the suggested support drawn to an agent which does not interfere with the specific binding of a ligand to any integrin since the support is only drawn to fold-affinity and specific affinity is defined by the specification only as the ability of two molecules to "associate" with each other. The subject matter claimed in claims 86. 96 and 116 broadens the scope of the invention as originally disclosed in the specification.

12. If Applicant were able to overcome the 35 USC 112 rejections above, Claims 80-120 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an agent that specifically binds to alpha 5 beta 1 integrin, does not reasonably provide enablement for an agent that binds to alpha 1-beta 5 two fold, five, fold or ten fold greater than any other integrin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to agents that bind to alpha 5 beta 1 integrin two fold, five, fold or ten fold greater than any other integrin. Since the specification does

not define selective binding or define specific binding in limiting terms, that is in terms of fold-affinity (since specific binding is defined only as the ability to of two molecules to "associate" with each other), it is assumed for examination purposes that the art recognized definition of WO95/14714 is the art recognized definition of the term, that is that "selective binding" refers to a 10-fold higher affinity for one integrin as compared to another and that "specific binding" refers to 100-fold high affinity for one integrin as compared to another, page 12 lines 18-30.

The specification teaches that fibronectin is selective for alpha 5 beta 1 integrin and that antibodies directed against the central cell binding fragment of fibronectin which contains the RGD integrin binding site inhibit angiogenesis and that these antibodies are likely to interfere with the specific binding of alpha 5 beta 1 integrin (p. 15, lines 3-15) and teaches that a variety of antagonists can interfere with the specific binding of alpha 5 beta 1 integrin with its ligands, particularly fibronectin and can reduce or inhibit angiogenesis (p. 18, lines 6-22). Methods for determining binding affinity and specificity are well known in the art (p. 18, last para), an inhibitor can act as a competitive inhibitor or a noncompetitive inhibitor of binding (last para, p. 19) and that antibodies for performing the method are those that bind at least an order of magnitude greater than they bind another integrin (p. 22) and that peptides of the invention are useful when they bind at least two-fold, five-fold and one order of magnitude greater specificity for alpha 5 beta 1 than for another integrin (p. 23) and exemplifies the method with the administration of anti-alpha 5 beta 1 antibody, SEQ ID NO:1 and nonpeptide SJ749 (which was

ineffective in CAM assay as well as in skin engraftment in SCID mice with anti-alpha 5 beta 1 antibody.

One cannot extrapolate the teaching of the specification to the scope of the claims because it is clear that both the antibody and SEQ ID NO:1 specifically bind alpha 5 beta 1 (wherein specific binding is defined by WO95/14714) it must be assumed that selectivity here is at least 100 fold over other integrins. Since no information is available about the specificity of the binding of the nonpeptide, the binding of this molecule cannot be assessed. However, it is clear that there is neither guidance on nor exemplification of any "agent" that does not have at least 100 fold binding to alpha 5 beta 1 integrin. It would be expected that if the "agent" does not bind to its target with high affinity that it would be sequestered by the targets to which it does have affinity. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The agent may be inactivated *in vivo* before producing a sufficient effect, for example, by proteolytic degradation, immunological activation or due to an inherently short half life of the agent. In addition, the agent may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the agent has no effect, circulation into the target area may be insufficient to carry the peptide and a large enough local concentration may not be established. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the

efficacy of the claimed methods with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed inventions with a reasonable expectation of success.

Objections

13. Objection drawn to the specification in Paper No. 9, Section 4, page 2 is maintained as Applicant has not amended the specification to reflect the abandonment of the provisional application.

14. All other objections and rejections raised in Paper No. 9 are withdrawn.

15. No claims allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
November 14, 2001